REMARKS

Claims 1, 4-13, 15-21, and 24-27 are pending and under examination. Claim 14 is withdrawn from consideration.

Applicants have amended claims 1, 12, and 24-26 to recite a "DT40 cell" or a method of inducing homologous recombination "in a DT40 cell." The specification supports this amendment at, for example, originally filed claim 2 and U.S. Patent Application Publication No. 2006/0099678 (which is the publication of the application as filed), paragraphs [0019], [0037], and [0078]. Due to this amendment, Applicants have canceled dependent claims 2, 22, and 23, which recited methods wherein the cell was a DT40 cell.

Applicants have also amended claims 1, 15, 26, and 27 to recite a method of homologous recombination or a vector "wherein there is no transcription promoter located 5' to the DNA sequence." The specification supports this amendment at, for example, Figure 1 and paragraphs [0020], [0021], [0022] and [0023]. Figure 1 illustrates a construct where there is no promoter 5' to the EGFP DNA sequence. Moreover, the cited portions of the specification demonstrate that only the gene has an upstream promoter that promotes transcription activity of the gene, while the "DNA sequence" does not.

Accordingly, these amendments do not add new matter, and Applicants respectfully request their entry.

Claims 1, 4-13, 15-21, and 24-27 are rejected under one or more of 35 U.S.C. §§ 102(b) and 103(a). Applicants address these rejections below.

Rejection under 35 U.S.C. § 102

The Office maintains the rejection of claims 1, 5, 7, 12-15, 17, and 25-27 under 35 U.S.C. § 102(b) as allegedly anticipated by Chauhan et al., *Gene*, 120: 281-286 (1992). According to the Office, Chauhan teaches:

> [A] vector comprising a gene and a DNA sequence and a promoter for controlling transcription of the gene, wherein the order is the DNA sequence, the transcription promoter 3' to the DNA sequence, and the gene 3' to the transcription promoter, wherein the DNA sequence has 60% or greater sequence identity to the gene.

Office Action, p. 2. The Office further alleges that "[t]he reference discloses a method comprising inserting said vector into a cell." *Id.* Apparently relying on the doctrine of inherent anticipation, the Office concludes, without citation, that "[h]omologous recombination would occur between the homologous DNA sequences." *Id.*

Solely to facilitate prosecution and without acquiescing to the rejection, Applicants have amended independent claims 1 and 26 to recite a method of inducing homologous recombination that occurs at a "genetic locus in a DT40 cell." Applicants have also amended claims 12 and 25 to recite a "DT40 cell." Chauhan does not teach use of the "DT40 cell," let alone "homologous recombination" in it. Moreover, Applicants have amended independent method claims 1 and 26 and independent vector claims 15 and 27 to recite "wherein there is no transcription promoter located 5' to the DNA sequence." Chauhan does not teach a method of inducing homologous recombination or a vector "wherein there is no transcription promoter located 5' to the DNA sequence." Indeed, as set forth in Figure 1, the pSSC-9 vector does include a transcription promoter located 5' to the upstream thymidine kinase gene. Accordingly, because

Chauhan does not teach each and every element of independent claims 1, 15, 26, and 27, this reference cannot anticipate claims 1, 5, 7, 12-15, 17, 25-27 under 35 U.S.C. § 102(b). Applicants therefore request that the Office withdraw this rejection.

Rejection under 35 U.S.C. § 103

The Office continues to reject claims 1, 5, 7, 12-15, 17, and 25-27 under 35 U.S.C. § 103(a) as allegedly obvious over Nickoloff et al., *Mol. Cell. Biol.*, 12:5311-5318 (1992) ("Nickoloff"). The Office alleges that:

> Nickoloff et al. disclose a method for inducing homologous recombination of mammalian cells, wherein the efficiency of the homologous recombination of a neo gene for example, which has been embedded in the chromosome of a mammalian cell such as a CHO cell, and regulated by a DEX reactive MMTV promoter, and a different neo gene or the like is enhanced by activating transcription from the aforementioned DEX-reactive MMTV promoter.

Office Action, p. 4. The Office further states that "[t]he reference discloses embodiments in which the order of the elements is DNA sequence comprising the promoter MMTV, the neo' gene sequence, followed by a neo encoding gene (see Fig. 1, 5)." *Id.* The Office asserts that "[t]he reference discloses that transcription enhances recombination between direct and inverted repeats and requires transcriptional activity in only one repeat, and when both repeats are transcriptionally active." *Id.* The Office alleges that "[t]herefore, it would have been obvious to one of ordinary skill in the art that transcription (i.e. placement of an active promoter at the 5' region) of either repeat would be encompassed." *Id.*

In making a rejection under 35 U.S.C. § 103, the Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142. The

key "to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." *Id.*; *see also KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." M.P.E.P. § 2142.

Moreover, to satisfy the initial burden of establishing a *prima facie* case of obviousness, the Office must make a determination whether the claimed invention "as a whole" would have been obvious to a person of skill in the art. M.P.E.P. § 2142. In this analysis, "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. *Id.* Further, the prior art must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. M.P.E.P. § 2141.02.

Responding to Applicants' arguments in the response filed on March 30, 2010, that it would not be obvious to modify Nickoloff by moving the MMTV promoter to regulate the downstream neo gene, the Office asserts that "Nicoloff et al. discloses the known effect of increased homologous recombination between a genetic element when transcription of said genetic element is activated." Office Action, page 4. Based solely on this, the Office concludes that "the particular placement of the genetic element of interest, promoter, and genetic element with which homologous recombination is desired, would have been obvious to one of ordinary skill in the art." *Id.* Applicants respectfully submit, however, that the Office has failed to establish a *prima facie* case of obviousness. The assertion that "Nicoloff et al. discloses the known effect of increased

homologous recombination between a genetic element when transcription of said genetic element is activated" does not provide any basis for the Office's conclusion that "the particular placement of the genetic element of interest, promoter, and genetic element with which homologous recombination is desired" would be obvious. Moreover, the Office has not pointed to any other rationale to support this conclusion. Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facia* case of obviousness.

Furthermore, Applicants respectfully submit that the Office has failed to consider Nickoloff as a whole. As noted in Applicant's previous reply, each of the constructs disclosed in Nickoloff includes a transcriptionally active upstream neo gene. More specifically, each construct includes an MMTV promoter placed at the 5' end of the upstream neo gene. *See* Figures 1, 5, and 6. Nickoloff does not provide any examples where a promoter is absent from the 5' end of the upstream neo gene. Moreover, Nickoloff shows only one construct where the downstream neo gene included a promoter. *See* Figure 6, illustration C. But the promoter in this construct is located 3' to the downstream inverted neo sequence, not 5' to the downstream sequence. Even in this construct, however, the upstream neo gene still includes a promoter at the 5' end of the gene.

Thus, when properly considered as a whole, it is clear that Nickoloff consistently contemplates a promoter at the 5' end of the upstream neo gene and does not provide any motivation or reasonable expectation to one of ordinary skill that the prior art could be modified to arrive at the claimed invention. Contrary to the Office's conclusion, Nickoloff's single statement that enhanced recombination "requires transcriptional

activity in only one repeat" does not suggest or provide a reasonable expectation that the prior art could be modified to arrive at the claimed invention. To the contrary, when Nickoloff is properly considered as a whole, it is clear that this statement merely stands for the proposition that transcription of the upstream neo gene is itself sufficient to enhance recombination. This is simply irrelevant to the claimed invention. Nor does Nickoloff's unsupported statement that "[p]reliminary data indicate that similar effects are found when both repeats are transcriptionally active" alter this conclusion in any way, as this still requires transcription of the upstream gene. Thus, Applicants respectfully assert that when properly considered as a whole, it is clear that Nickoloff does not provide any motivation or reasonable expectation to one of ordinary skill to modify the prior art to arrive at the claimed invention. Accordingly, Applicants respectfully submit that the Examiner's contrary conclusion is based on improper hindsight reasoning.

Solely to advance prosecution, however, Applicants have amended independent method claims 1 and 26 to recite a method of inducing homologous recombination at a genetic locus "in a DT40 cell . . . wherein there is no transcription promoter located 5' to the DNA sequence." Applicants have also amended claims 12, 24, and 25 to recite a "DT40 cell." Furthermore, Applicants have amended independent vector claims 15 and 27 to recite a vector "wherein there is no transcription promoter located 5' to the DNA sequence." Nickoloff does not teach a method of inducing homologous recombination in a DT40 cell. Moreover, Nickoloff does not suggest a method of homologous recombination or a vector wherein there is no transcription promoter located 5' to the DNA sequence. Indeed, far from suggesting such a method or vector, Nickoloff

consistently describes an MMTV promoter located 5' to the upstream neo gene and provides no motivation or reasonable expectation to modify the prior art to arrive at the claimed invention. Accordingly, Applicants request that the Office withdraw this objection.

The Office also continues to reject claims 2, 8, 18, and 23 under 35 U.S.C. § 103(a) as unpatentable over Nickoloff in further view of Lahti et al., *Methods: A Companion to Methods in Enzymology*, 17, 305-312 (1999). Office Action at page 5. Acknowledging that Nickoloff does not discuss a DT40 cell line and a tetracycline inducible promoter, the Office states that Lahti discloses DT40 cells "and discloses that said cells have higher rates of homologous recombination than other cell types, and disclose transcription of genes therein by means of a tetracycline-reactive promoter." *Id.* The Office asserts that "[i]t would have been obvious to have used a cell type such as DT40 which has increased levels of homologous recombination, in the method disclosed by Nickoloff et al. in order to obtain said higher levels of recombination." *Id.*

The Office further continues to reject claims 9, 10, 19, and 20 under 35 U.S.C. § 103(a) as unpatentable over Nickoloff in further view of Slebos et al., *Biochemical and Biophysical Research Communications*, 281:212-219 (2001). Office Action at page 6. Acknowledging that Nickoloff does not disclose a gene and DNA sequence encoding EGFP or EBFP, the Office states that Slebos "discloses the EBFP and EGFP genes and their introduction into a mammalian cell such as a DT-40 cell." *Id.* Accordingly, the Office asserts that "[i]t would have been obvious to have used easily assayable genes, such as EGFP or EBFP as disclosed by Slebos, in a method of recombination and in a vector and cell used for said method." *Id.*

Moreover, the Office continues to reject claims 4, 6, 11, 16, 21, and 24 under 35 U.S.C. § 103(a) as unpatentable over Nickoloff in further view of Phi-van et al., *Biochemistry*, 35:10735-10742 (1996), or Israel et al., *Nucleic Acids Research*, 17:4589-4604 (1989). Office Action at page 6. Acknowledging that Nickoloff does not disclose a MAR, "which may be from the chicken lysozyme gene," or an enhancer, the Office asserts that Phi-van discloses "the MAR in the vicinity of the chicken lysozyme gene, and discloses a method for enhancing the expression of structural genes that are in the vicinity of the expression unit." *Id.* at page 7. Moreover, the Office asserts that Israel discloses "an MMTV enhancer region, which is present in the vicinity of the MMTV promoter." *Id.* The Office asserts that "[i]t would have been obvious to one of ordinary skill in the art to have included known elements, such as MAR and or enhancer regions, in the construct and method of Nickoloff." *Id.*

Finally, the Office continues to reject claim 22 under 35 U.S.C. § 103(a) as unpatentable over Nickoloff in view of Phi-van or Israel and further in view of Lahti. Office Action at page 7. The Office states that "Nickolof et al., Phi-van, Israel et al. are cited for the reasons set forth above," *id.*, but acknowledges that they do not disclose the use of DT40 cells. *Id.* The Office thus relies on Lahti to disclose DT40 cells that allegedly have higher rates of homologous recombination than other cell types.

All of these rejections rely on a combination of Nickoloff with the above cited references. For the reasons discussed above, however, Nickoloff does not provide any motivation or reasonable expectation to one of ordinary skill that the prior art could be modified to arrive at the claimed invention. Further, solely to advance prosecution, Applicants have amended independent claims 1, 15, 26, and 27 to recite a method of

homologous recombination or a vector wherein there is no transcription promoter located 5' to the DNA sequence. As discussed above, Nickoloff consistently teaches a promoter located 5' to the upstream sequence, and thus does not provide any motivation or reasonable expectation for a method of homologous recombination or a vector wherein there is no promoter located 5' to the upstream neo gene. Lahti, Slebos, Phi-van, and Israel do not cure this deficiency in Nickoloff. Thus, the combination of Nickoloff with Lahti, Slebos, Phi-van, and Israel does not render the claims obvious. Accordingly, applicants request that the Office withdraw these rejections.

Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 21, 2010

By:_____
Jared Schuettenhelm
Reg. No. 59,539
(650) 849-6752